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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,541	08/07/2000	Marcel Loetscher	2225.1001-010	3846

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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/633,541	LOETSCHER ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 18, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-48, 61, 62, 64, 65 and 67-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *30-48, 65, 69-98, and 102-108* is/are allowed.

6)☒ Claim(s) *61,62,64,67,68 and 99-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/18/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *PTO-1449 02/02/05*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 18, 2003 has been entered.

Formal Matters

Claims 30-39, 41-44, 46-48, 61, 62, 64, 65, 67-75, 77, 78, 80, 81 and 83-92 have been amended, and new claims 106-108 were added in the communication dated March 18, 2003.

Claims 49, 51, 52, 60, 63 and 66 were canceled. Currently, claims 30-48, 61, 62, 64, 65 and 67-108 are under consideration.

The rejections to claims 30-48, 65, 69-98, and 102-105 under 35 U.S.C. 112, first paragraph are withdrawn by the Examiner due to amendments by Applicants.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 7, 2000 and the supplemental information disclosure statements submitted on March 18, 2003 and on February 2, 2005 are in compliance with the provisions of 37 CFR 1.97. The IDS

submitted on August 7, 2000 was considered by examiner Murphy on February 22, 2002, and an initialized copy of said form is included in this office action. The supplemental information disclosure statements are currently being considered by the examiner.

Drawings

The drawings were received on September 25, 2000. These drawings are acceptable.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 61-62, 64, and 67-68 are rejected and claims 99-101 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection argues that while the specification and the art provides adequate written description for a method of detecting or identifying an agent which binds a human CXCR3 with an amino acid sequence as set forth in SEQ ID NO: 2, the specification fails to adequately describe a method of detecting or identifying an agent which binds an CXCR3 protein variant encoded by a nucleic acid sequence with at least 75% identity with SEQ ID NO: 1, or are encoded by a nucleic acid which hybridizes to SEQ ID NO: 1.

The skilled artisan cannot envision all of the nucleic acid sequences that have at least 75% identity with SEQ ID NO: 1 or that hybridize to SEQ ID NO: 1, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Only a method of detecting or identifying an agent which binds a human CXCR3 with an amino acid sequence as set forth in SEQ ID NO: 2 meets the written description provision of 35 U.S.C. § 112, first paragraph.

Applicants argue that 61-62, 64, 67-68 and 99-101 are supported by adequate written description with respect to claims that recite amino acid sequence identity and/or claims that recite hybridization conditions. Specifically, the claimed genus does not have substantial variation because the CXCR3 proteins or variants are encoded by a nucleic acid having at least about 75% with the coding region of SEQ ID NO:1, and have the specified binding activity. Applicants also argue that the disclosed human CXCR3 is representative of the genus because the members of the claimed genus are encoded by a nucleic acid having at least about 75% nucleotide sequence identity with the coding region of SEQ ID NO:1, and assays suitable for identifying CXCR3 proteins

or variants that have the specified binding activity are disclosed. Additionally, the disclosed domain structure of CXCR3 together with the art-recognized importance of the extracellular domains of chemokine receptors in ligand binding adequately correlates receptor structure and ligand binding activity, and further demonstrates to the person of skill in the art that Applicants were in possession of the claimed ligand binding variants.

Applicant argues that the specification contains an adequate written description of the claimed subject matter because the claims contain a function (binding IP-10 and Mig) and a structural limitation (80-90% homology, encoded by a nucleic acid which hybridizes to SEQ ID NO: 1). However, as Applicant points out, in Lilly the court held that one of two elements may satisfy a genus of CDNAS, i.e. i) a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or; ii) a recitation of structural features common to members of the genus, which features constitute a substantial protein of the genus. University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997). In the instant case, the first element is not met because only a CDNA encoding SEQ ID NO: 2 is disclosed. The second element requires structural features common to members of the genus, however, in the instant disclosures insufficient guidance is provided as to which are the critical residues which are necessary for the claimed protein function of binding IP-10 or Mig. Even at 90% homology, SEQ ID NO: 2 is 368 amino acids long, thus mutations could be introduced at up to ca. 37 amino acids, and each possible mutation is chosen from 20 possible amino acids. These claims encompass a very large number of possible members of the

genus (37 possible members, not including deletion mutants). Applicant points to the Written Description guidelines, which include an example of a claim having written description which is directed to a protein and variants thereof that are at least 95% identical, with a specific catalytic function. If the claims were amended to meet similar structural limitations, the rejection might be reconsidered.

Amended claims 61-62, 64, and 67-68 are rejected and claims 99-101 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting or identifying an agent which binds a human CXCR3 with an amino acid sequence as set forth in SEQ ID NO: 2, does not reasonably provide enablement for a method of detecting or identifying an agent which binds an CXCR3 protein variant encoded by a nucleic acid sequence with at least 75% identity or at least 90% identity with SEQ ID NO: 1, or are encoded by a nucleic acid which hybridizes to SEQ ID NO: 1.

Applicants argue that 61-62, 64, 67-68 and 99-101 are supported by adequate written description with respect to claims that recite amino acid sequence identity and/or claims that recite hybridization conditions. Specifically, the claimed genus does not have substantial variation because the CXCR3 proteins or variants are encoded by a nucleic acid having at least about 75% or at least 90% nucleotide sequence identity with the coding region of SEQ ID NO:1, and have the specified binding activity. Applicants also argue that the disclosed human CXCR3 is representative of the genus because the members of the claimed genus are encoded by a nucleic acid having at least about 75%

or at least about 90% nucleotide sequence identity with the coding region of SEQ ID NO:1, and assays suitable for identifying CXCR3 proteins or variants that have the specified binding activity are disclosed. Additionally, the disclosed domain structure of CXCR3 together with the art-recognized importance of the extracellular domains of chemokine receptors in ligand binding adequately correlates receptor structure and ligand binding activity, and further demonstrates to the person of skill in the art that Applicants were in possession of the claimed ligand binding variants.

Applicants' arguments are not found to be persuasive.

The claims are drawn to a method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof, wherein said mammalian CXCR3 protein or ligand biding variant is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of SEQ ID NO:1.

In the specification (page 14 line 23 to page 15, line 14), Applicants disclose that variants of the polypeptide includes deletions substitutions and variants, without disclosing any actual or prophetic examples on expected performance parameters of any of the possible muteins of CXCR3 protein. There is no guidance provided in the specification as to how one of ordinary skill in the art would practice a method of detecting or identifying an agent which binds an CXCR3 protein variant encoded by a nucleic acid sequence with 75% identity with SEQ ID NO: 1 other than those exemplified in the specification. Applicant argues that it would require routine experimentation to follow the guidelines set forth in the specification to prepare CXCR3

proteins or variants. However, as set forth *supra*, even at a 90% homology, SEQ ID NO: 2 is 368 amino acids long, thus mutations could be introduced at up to ca. 37 amino acids, and each possible mutation is chosen from 20 possible amino acids. These claims encompass a very large number of possible members of the genus (37^{20} possible members, not including deletion mutants). Additionally, there is insufficient guidance provided to indicate which amino acid residues are necessary for the CXCR3 function of binding IP-10 and Mig.

As an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, de1ta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype, thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and

assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Additionally, Yan et al. teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass a method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof, wherein said mammalian CXCR3 protein or ligand biding variant is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of SEQ ID NO:1, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims do not set forth a functional limitation for the mammalian CXCR3 protein or ligand biding variant and since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of any

encoded gene product are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass mammalian CXCR3 protein or ligand biding variant, it would require undue experimentation for one of skill in the art to make and use the claimed gene products. Since the claims do not enable one of skill in the art to make and use the claimed gene products, and since detailed information regarding the structural and functional requirements of the encoded gene products are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Given the large number of possible species encompassed by the claims, and the insufficient guidance provided in the specification as to the critical residues necessary for protein function, it would require undue experimentation of one of skill in the art to make and use the claimed invention.

Allowable Subject Matter

Claims 30-48, 65, 69-98, and 102-108 are allowed.

Conclusion

Claims 61-62, 64, 67-68 and 99-101 are rejected. Claims 30-48, 65, 69-98, and 102-108 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on M-F: 8:30am – 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory S. Emch, Ph. D.
Patent Examiner
Art Unit 1646
June 7, 2005

JOSEPH MURPHY
PATENT EXAMINER